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<p>(21) International Application Number: PCT/EP99/03677 (22) International Filing Date: 27 May 1999 (27.05.99)</p> <p>(30) Priority Data: 60/086,895 27 May 1998 (27.05.98) US</p> <p>(71) Applicant (<i>for all designated States except US</i>): EUROCELTIQUE S.A. [LU/LU]; 122, boulevard de la Petrusse, Luxembourg (LU).</p> <p>(72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): FLEISCHER, Wolfgang [DE/DE]; Posener Strasse 6, D-55218 Ingelheim (DE). REIMER, Karen [DE/DE]; Im Rehwinkel 12, D-65582 Hambach (DE).</p> <p>(74) Agent: MAIWALD, Walter; Maiwald GmbH, Elisenhof – Elisenstrasse 3, D-80335 München (DE).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: PREPARATIONS FOR THE APPLICATION OF ANTI-INFLAMMATORY, ESPECIALLY ANTISEPTIC AGENTS AND/OR AGENTS PROMOTING THE HEALING OF WOUNDS, TO THE UPPER RESPIRATORY TRACT AND/OR THE EAR</p> <p>(57) Abstract</p> <p>Use of anti-inflammatory agents such as povidone iodine for the preparation of a pharmaceutical composition for the treatment of diseases of the upper respiratory tract and/or the ear which are susceptible to the administration of such agents.</p>		

Preparations for the application of anti-inflammatory, especially antiseptic agents and/or agents promoting the healing of wounds, to the upper respiratory tract and/or the ear

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The invention concerns preparations for the application of agents with anti-inflammatory, especially antiseptic and/or wound healing promoting properties to the upper respiratory tract and/or the ear. The preparations are specifically applied to wounds, skin, mucous membranes and mucosa-like unkeratinized epithelial, especially ciliary epithelial tissues in the upper respiratory tracts and/or the ears of humans and animals.

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Furthermore, the invention concerns a method of preventing or treating infections by applying a pharmaceutical preparation.

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A plurality of different antibiotic and antiseptic agents are known for the topical treatment of infectious maladies. A decisive disadvantage of antibiotic agents is that the infecting bacteria show primary resistances, and can acquire secondary resistances, against these agents. Further, antibiotics quite often lead to patient sensibilisation. The use of e.g. halogen-releasing antiseptics such as povidone iodine, also known as polyvidone iodine or PVP-iodine, i.e. the poly(1-vinyl-2-pyrrolidin-2-one)-iodine complex, can prevent resistances. Antiseptic agents are also much more rarely allergenic as compared to antibiotics.

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At present, infectious diseases of the respiratory tract are treated with antibiotics. The application of antibiotic agents via the respiratory tract has been the subject of several reviews and articles with an emphasis, however, on the lower respiratory tract. Ramsey et al., for example, describe the intermittent administration of inhaled tobramycin in patients with cystic fibrosis in "The New England Journal

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liposomes" (H. Schreier, in "Journal of Controlled Release", 24, 1993, p.209-223). The physicochemical characterization of liposome aerosols and also their therapeutic applications to the respiratory tract are shown therein. Drugs that have been investigated for pulmonary delivery via liposomes include, e.g. anti-cancer agents, peptides, enzymes, anti-asthmatic and anti-allergic compounds and, as mentioned above, also antibiotics. The formulation of liposome aerosols or liposome powder aerosols using, for example a dry powder inhaler has also been described by H. Schreier in "Formulation and in vitro performance of liposome powder aerosols" (S.T.P. Pharma Sciences 4, 1994, p.38-44).

10 Although a lot of attention has been paid to liposomes as drug carriers, as can be seen from the cited documents, there appears to be no prior art relating to liposomes and other particulates as carriers of anti-inflammatory, especially antiseptic and/or wound-healing promoting agents for applications in the body, especially in the upper respiratory tract, including the mouth, throat and nose, and in the ear.

20 Most of the prior art cited above is concerned with liposome preparations. It should be understood that alternative drug carriers of a similarly particulate character exist. These drug carriers can often -and also in the context of this invention- be used instead of liposomes and include microspheres (generally comprising lipophilic polymers), nanoparticles, "Large Porous Particles" and individually coated drug substance molecules, e.g. made by using pulsed laser deposition (PLD) techniques. These PLD methods can be used to apply coatings 25 to drug powders and to modify surface properties and release rate to a variety of drug systems.

Where hereinafter reference is made to liposomes or particulate carriers, it is to be understood that this is to incorporate such alternative carriers, too.

excluding the external facial skin areas of mouth and nose. The upper respiratory tract thus comprises those parts which may be considered to be inside the body. In the same context, the ear is considered to broadly include those parts of the ear which lie inside the skull, but are accessible from the outside thereof. Generally, 5 this will include the passages of the outer ear and, in some cases, the middle ear, but will exclude the inner ear and also those parts of the outer ear which surround the ear orifice, on the outside of the skull.

10 In the context of this invention, anti-inflammatory agents are understood to include antiseptic agents, antibiotic agents, corticosteroids, and wound-healing agents, as defined below.

15 In the context of this invention, antiseptic agents are understood to include those disinfecting agents which are pharmaceutically acceptable and suitable for the treatment of the upper respiratory tract to the extent that they can be formulated in accordance with the invention.

20 More specifically, antiseptic agents include inter alia oxygen- and halogen-releasing compounds; metal compounds, e.g. silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.

25 Wound-healing agents comprise agents promoting granulation and epithelialization such as dexamphenol, allantoin, azulenes, tannines, and vitamine B-type compounds.

One object achieved by the invention is therefore concerned with improved tissue repair in the body. The invention achieves this by the application of anti-inflammatory agents, in the form of a particulate carrier preparation as defined in the independent claims.

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The anti-inflammatory, antiseptic and/or wound-healing preparation can be administered to the respiratory tract by a nebulization agent loaded of the particulate carrier preparation, or by dry powder inhalation of the respective preparation. For example, a liposome preparation can be made by loading

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liposomes with PVP iodine in a conventional procedure.

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It is also possible to compact the loaded liposomes, optionally together with auxiliary materials, such as low molecular sugars, preferably lactose, to a tightly compacted solid medicament reservoir. This medicament stock can then be abraded or micronized or treated in other ways to yield the powder in particle form. The resulting liposome preparation can be administered by inhalation of the preparation in the form of a powder aerosol, as, for example, described in "Acute Effects of Liposome Aerosol Inhalation on Pulmonary Function in Healthy Human Volunteers" (Thomas et al., Preliminary report, Volume 99, 1991, p. 1268-1270).

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The pressures for preparing the tightly compacted solid medicament stock are preferably in the range of from 50-500 MPa. Such medicament stock is described in WO 94/14490 and a device for administration is disclosed in WO 93/24165.

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The nature or constitution of the liposomes is generally not critical. The liposome preparation as, for example, described in EP 0 639 373 can be administered to the nose or the throat as an aerosol, e.g. a pump spray. For applications in the mouth cavity, the inventive preparations are preferably formulated as a pump spray, a gel, or a rinsing solution. The disclosure of EP 0 639 373 is incorporated by reference.

uniform liposome size.

The average size of the liposomes according to this invention can vary over a broad range, generally from about 1 to about 20,000 nm. Liposomes with 5 diameters in the range of about 50 and 4,000 nm are preferred. Liposomes with diameters at around 1000 nm are presently most preferred for e.g. gel applications. For solutions, smaller average diameters may be more suitable.

Where alternative particulate carriers are used, they are generally prepared as 10 known in the art. Thus, microspheres which are used to deliver a very wide range of therapeutic or cosmetic agents, are made as described for example in WO 95/15118.

Nanoparticles may in some cases be used, provided that they can be loaded with a 15 sufficient amount of active agent and can be administered to the lower respiratory tract according to this invention. They can be prepared according to the methods known in the art, as e.g. described by Heyder (GSF München) in "Drugs delivered to the lung, Abstracts IV, Hilton Head Island Conference, May 1998.

20 Methods using a pulse laser deposition (PLD) apparatus and a polymeric target to apply coatings to drug powders in a short non-aqueous process are also suitable for the formation of particulate preparations according to this invention. These have e.g. been described by Talton et al., "Novel Coating Method for Improved Dry Delivery", Univ. of Florida UF 1887 (1998).

25 A further suitable delivery system employs Large Porous Particles as disclosed by David A. Edwards et al. in "Large Porous Particles for Pulmonary Drug Delivery" (Science, 20. June 1997, Vol. 276, p 1868-1871).

Generally, the concentrations in the preparation, particle sizes, active agent loadings etc. will be selected for such alternative carriers to correspond basically to the parameters discussed herein with respect to liposome preparations. Selecting and providing such parameter based inter alia on straightforward experimentation, is well within the skill of an ordinary worker experienced in this art.

A presently highly preferred use of the inventive liposome preparations is in the local treatment of infections of the nose, mouth and throat, especially when the liposome preparations contain povidone iodine. Also in this indication, the inventive antiseptic preparations, especially those containing PVP iodine, have the great advantage of not causing resistances and lead to much less allergic reactions, while permitting a very cost-efficient therapy with a broad spectrum of effect. A povidone iodine liposome preparation according to this invention is e.g. effective against viruses, such as herpes simplex. This effect is not provided by antibiotic agents. Further, a liposome preparation of a microbicidal agent such as povidone iodine provides protracted release of the agent from liposomes in the nasal or oral mucosa. This leads to extended effect of the antimicrobial substance, and thus less frequent application, as compared with the customary antiseptic solution preparations.

The present invention is also useful in the treatment of infectious diseases or for alleviation of diseases such as HIV infections which are accompanied by opportunistic infections. Also patients having a suppressed immune system, for example, after organ transplants, can be treated according to the invention. In particular, acute and chronic laryngopharyngitis and angina can be treated with the povidone iodine preparation according to the invention.

preparation.

In a lotion, which can be a hydrophilic or a lipophilic lotion, a typical range of active agent will be between 0.5 and 10 g agent, and between 1 and 5 g, 5 preferably about 4 g of liposome membrane forming agent such as hydrogenated soy bean lecithine, per 100 g of lotion. In the case of a hydrophilic lotion, electrolyte solution will often be used in preparing the liposome containing lotion. A lipophilic lotion will often be made from agent, membrane forming substance and lipophilic formation agents such as medium chain length triglycerides etc.

10 A hydrophilic cream comprising an inventive liposome preparation will generally comprise between 0.1 and 10 g agent, such as povidone iodine, together with between about 1 and 10 g membrane forming substance and further typical O/W cream forming additives, per 100 g of cream.

15 A comparable amphiphilic cream according to the invention will have similar contents of agent and membrane forming substance such as lecithine, and will have the typical further additives of an amphiphilic cream.

20 A hydrophilic ointment according to the invention can broadly comprise between 0.1 and 10 g agent and between 1 and 10 g liposome membrane forming substance such as lecithine, together with typical prior art ointment basis substances such as Macrogol (TM) and water, in 100 g of ointment.

25 A non-alcoholic hydrogel according to the invention could broadly comprise between 1 and 5 g agent such as povidone iodine, approximately 2 g lecithine and gel forming substances such as Carbopol (TM), with pH-adjusting agent and water to form 100 g of hydrogel.

An aqueous system is prepared from electrolyte components and the (one or more) active agents to be incorporated in the liposome preparation. Such an aqueous system can e.g. comprise 10 mmol/l sodium hydrogen phosphate and 0.9 % sodium chloride, at pH 7.4; the aqueous system will further comprise at least the 5 desired amount of the active agent, which in the embodiment examples is povidone iodide. Often, the aqueous system will comprise an excess amount of agent or agents.

The liposomes are generally formed by agitating said aqueous system in the 10 presence of said film formed by the lipid components. At this stage, further additives can be added to improve liposome formation; e.g. sodium cholate can be added. Liposome formation can also be influenced by mechanical action such as pressure filtration through e.g. polycarbonate membranes, or centrifuging. Generally, the raw liposome dispersion will be washed, e.g. with electrolyte 15 solution as used in preparing the above-described solution of the active agent.

When liposomes with the required size distribution have been obtained and washed, they can be redispersed in an electrolyte solution as already described, often also comprising sugars such as saccharose or a suitable sugar substitute. 20 The dispersion can be freeze-dried, and it can be lyophilised. It can, prior to use, be reconstituted by addition of water and suitable mechanical agitation at the transition temperature of the lipid component, which for hydrogenated soy bean lecithine is e.g. 55°C.

25 In the following Examples, hydrogenated soy bean lecithine (EPIKURON (TM) 200 SH obtainable from Lukas Meyer, Germany or PHOSPOLIPON (TM) 90 H obtainable from Nattermann Phospholipid GmbH, Germany) was used. However, other pharmaceutically acceptable liposome membrane forming substances can be used instead, and the person skilled in the art will find it easy to select suitable

After the last centrifugation step and discarding of the supernatant, sodium chloride buffer solution was added ad 12 ml, and the liposomes were homogenously distributed therein. The product was then distributed into vials each containing 2 ml liposome dispersion, and the vials were then subjected to a 5 freeze-drying step.

After the freeze-drying, each vial comprised about 40 mg solids.

The method of Embodiment Example I has a minor disadvantage in that the PVP 10 iodine solution used, due to the high percentage of solids, is rather viscous and thus more difficult to handle.

Embodiment Example II

15 In a 2000 ml flask provided with glass beads to increase surface, 173 mg hydrogenated soy bean lecithine and 90 mg disodium succinate were dissolved in approximately 60 ml of a methanol/chloroform mix in a 2:1 ratio. The solvent was removed under vacuum until a film was formed.

20 4 g PVP iodine (10 % available iodine) were dissolved in 40 ml of the sodium chloride buffer solution described in Embodiment Example I, and were added to the lipid film in the flask. The flask was then shaken until the film dissolved and liposomes were formed.

25 The product was centrifuged and the supernatant liquid was discarded.

To the thus produced liposome pellet, further sodium chloride buffer solution was added ad 40 ml, and the centrifuging step was repeated. The supernatant was again discarded. At this stage, this washing step could be repeated where

were mixed with 4 g Polysorbate 40 (TM), 8 g cetylstearyl alcohol, 8 g glycerol, 24 g white vaseline, and water ad 100 g.

Embodiment Example IV

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An amphiphilic cream was prepared from 10 g hydrogenated soy bean lecithine/povidone iodine liposomes as described in Embodiment Example II; 7.5 g medium chain length tryglyceride, 7 g polyoxyethyleneglycerol monostearate, 6 g cetylstearyl alcohol, 8 g propylene glycol, 25 g white vaseline, and water ad 100 g.

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g.

Embodiment Example V

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A hydrophilic ointment which can be rinsed off with water was prepared using 10 g of liposomal PVP iodine as described in Embodiment Example II, 55 g Macrogol 400 (TM), 25 g Macrogol 4000 (TM), and water ad 100 g.

Embodiment Example VI

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A hydrogel was prepared from 4 g liposomal PVP iodine as described in Embodiment Example II, 0.5 g Carbopol 980 NF (TM), sodium hydroxide ad pH 7, water ad 100 g.

Further modifications of the above-described embodiments are envisaged.

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Thus, the creams of Embodiment Examples III and IV can have an additional content of an agent known to promote the healing of wounds, such as allantoin. Such an agent will be added in a pharmaceutically useful concentration, in the case of allantoin in the range of 0.1 to 0.5 g, per 100 g of cream. The wound-

5 The reservoir is sealed by a closure element which can move through the reservoir like a piston moves in a cylinder. By the stepwise emptying of the reservoir, this closure element is sucked into the reservoir, so that the remaining amount of pharmaceutical preparation in the reservoir is always sealed off, while at the same time the reservoir can be emptied.

Such a device is useful for pasty preparations, creams, ointments etc.

10 In a two-chamber gas pressure pack, the pharmaceutical preparation is contained in a bag of flexible plastics film material. Often, this is high pressure 15 polyethylene.

The bag is contained inside a gas tight pressure vessel which further contains a supply of pressurizing gas, very often a compressed inert gas like nitrogen or air.

15 The plastic film bag has only one outlet, which is gas-tightly connected to the interior wall of the pressure vessel, surrounding a single opening thereof. The pressurized gas in the vessel tends to compress the bag, driving the pharmaceutical preparation inside the bag out through the opening of the bag and thus through the 20 opening of the vessel. A valve and, in case, spray-head device is provided in the vessel mouth. Operating the valve releases a spray mist, a jet of liquid or a portion of flowable solid such as cream. Using such a system, solutions, emulsions, creams, ointments and gels can be dosed and applied.

25 Using inventive preparations efficiency tests were then carried out, as follows:

Microbiology and Infection Diseases, Berlin, March 1999. In cell cultures, liposomal PVP-iodine is highly effective against herpes simplex virus type 1 and adenovirus type 8, while the long-term cytotoxicity experiments indicated that the liposomal form is better tolerated than aqueous PVP-iodine by the majority of cell lines tested. PVP-iodine in liposomal form is not genotoxic.

Test III

10 A 3% PVP-iodine hydrogel liposomal preparation was compared with a 3% PVP-
iodine ointment, where the active agent was not in liposomal form. The agent
was applied to standardized in vitro cultures of rat skin and peritoneal explants, as
a screening for tissue compatibility of skin and wound antiinfectives.

15 The growth rate of the cultured explants was studied after 30 minutes exposure
and incubation with a test substance.

Again, the substantially better toleration of the liposomal preparation was clearly shown in the results, in terms of peritoneum growth rate and skin growth rate.

With the ointment, the peritoneum growth rate reached 85%, and the skin growth rate reached 90%; with the liposomal hydrogel formulation, the peritoneum growth rate was 96%, and the skin growth rate was 108%; these values are to be compared with 100% values in a control test using Ringer's solution as the agent.

25 Test IV

The toleration of liposomal PVP-iodine solutions for nasal applications was studied by investigating the influence of different test substances on ciliated epithelium cells, the most sensible cells of the mucous membrane. A cytotoxic

Claims

1. A process for the manufacture of a pharmaceutical preparation for the application of anti-inflammatory, especially antiseptic agents and/or agents which promote the healing of wounds to the upper respiratory tract and/or the ear, characterised in that the preparation contains at least one of said agents combined with a particulate carrier.
2. The process of claim 1, characterised in that said particulate carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a Large Porous Particle preparation, or a laser-pulse polymer coated molecule preparation.
3. The process according to claim 1 or 2, characterised in that at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere carrier.
4. The process of any one of claims 1 to 3, characterised in that the anti-inflammatory agent is an antiseptic agent, an antibiotic, a corticosteroid, or a wound-healing promoting agent.

9. The process according to any one of the preceding claims,
characterised in that the preparation contains at least one antiseptic and at least
one wound-healing promoting agent.

5 10. The process according to any one of the preceding claims,
characterised in that the carrier particles, especially liposomes, have a substantially
uniform size in the range between about 20 and about 20,000 nm, preferably in
the range between about 50 and about 4,000 nm, more preferably between 500
and 2,500 nm and especially preferably a uniform size of about 1,000 nm
10 diameter.

11. The process according to any one of the preceding claims,
characterised in that the carrier, especially liposome, preparation releases the agent
over an extended time period, preferably an extended time period of several hours
15 duration.

12. The process according to claim 11,
characterised in that the carrier, especially liposome, preparation releases the agent
at approximately the same release rate over the release time period.

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13. The process according to any one of the preceding claims,
characterised in that the preparation additionally comprises at least one

18. The process according to any one of claims 1 to 14, the preparation being in the form of a pharmaceutical gel, especially a non- alcoholic hydrogel containing the carrier and agent or agents in a pharmaceutically acceptable hydrogel basis.

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19. The process according to any one of claims 1 to 14, the preparation being in the form of a spray containing the carrier and agent in a pharmaceutically acceptable sprayable solid or liquid formulation.

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20. The process according to any one of the preceding claims, the preparation being in the form of a pharmaceutical solution or dispersion formulation, which comprises:

- a) liposomes comprising a pharmaceutically acceptable liposome membrane forming substance; and
- 15 b) a 0.1 to 2 % PVP iodine solution (at approximately 10 % available iodine in the PVP iodine complex) at least most of which is encapsulated by said liposome membranes,

20 wherein the liposomes are of substantially uniform size between about 50 and about 4,000 nm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical solution or dispersion formulation.

with a particulate carrier in said preparation.

26. The method of claim 25, wherein said carrier comprises at least one of a liposome preparation, a microsphere preparation, a nanoparticle preparation, a
5 Large Porous Particle preparation or a laser-pulse polymer coated molecule preparation.

27. The method of claim 25, wherein at least the greatest part of said agent is encapsulated inside the carrier, especially a liposome or microsphere
10 carrier.

28. The method of claim 25, wherein the anti-inflammatory agent is selected from antiseptic agents, antibiotics, corticosteroids and wound-healing promoting agents.

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29. The method of claim 25, wherein the antiseptic agent is selected from oxygen- and halogen-releasing compounds; metal compounds, such as silver and mercury compounds; organic disinfectants including inter alia formaldehyde-releasing compounds, alcohols, phenols including alkyl- and arylphenols as well as halogenated phenols, quinolines and acridines, hexahydropyrimidines, quaternary ammonium compounds and iminium salts, and guanidines.
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35. The method of claim 25, wherein the carrier, especially liposome, preparation releases the agent over an extended time period, preferably an extended time period of several hours duration.

5 36. The method of claim 25, wherein the carrier, especially liposome, preparation releases the agent at approximately the same release rate over the release time period.

10 37. The method of claim 25, wherein the preparation additionally comprises at least one anaesthetically active agent.

38. The method of claim 25, wherein the preparation contains additives and adjuvants such as conserving agents, antioxidants and consistency-forming additives.

15 39. The method of claim 25, the preparation being in the form of a solution or dispersion comprising the active-agent loaded carrier, especially in the form of liposomes, preferably in the form of a liquid pharmaceutical preparation.

20 40. The method of claim 25, the preparation being in the form of a hydrophilic or amphiphilic cream, comprising the carrier and agent formulation in a hydrophilic or amphiphilic cream base, or in the form of a pharmaceutical O/W

and about 4,000 nm, and, in case, the formulation additionally comprises customary additives, adjuvants and auxiliary substances of a pharmaceutical solution or dispersion formulation.

5 45. The method of claim 25, wherein the liposomes are of substantially uniform size, with diameters at around 1,000 nm, and the preparation is a gel.

10 46. The method of claim 25, wherein the preparation is suited for the treatment of infectious diseases or alleviation of diseases such as HIV infections which are accompanied by opportunistic infections or a suppressed immune system.

15 47. The method of claim 25, wherein the preparation is suited for the treatment of laryngopharyngitis, angina and/or rhinitis.